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10/808,004	03/24/2004	Mary L. Owens	58516US003	4652

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EXAMINER
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FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.



## DETAILED ACTION

### *Response to the Amendment*

The Amendment filed on 9/25/2006 in response to the previous Non-Final Office Action (4/06/2006) is acknowledged and has been entered.

Claims 1 and 7-16 are currently pending and under consideration.

The Declaration filed on 9/25/2006 under 37 CFR 1.131 is sufficient to overcome the rejection of claims 1-16 under 35 U.S.C. 102(a) as being anticipated by Shumach et al. (Arch. Dermatol. 38: 1165-1171), as well as the Geisse et al. (J. Am. Acad. Dermatol. 2002; 47: 390-398) reference used in the rejection of claims 1-12 and 15 under 35 U.S.C. 103 (a).

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

### **Rejections Maintained:**

#### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 7-12 and 16 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Marks et al. (J. Am. Acad. Dermatol. 2001; 44: 807-813, IDS) or Beutner et al. (J. Am. Acad. Dermatol. 1999; 41: 1002-1007, IDS) or Kagy et al. (Dermatol. Surg. 2000; 26: 577-579).

Marks et al teach a method of treating superficial basal cell carcinoma comprising administering an effective amount of imiquimod 5% cream. With regards to the administration cycle, the reference teaches that nine patients were randomized to 6 weeks' application of iminiquimod in 1 of the 4 treatment cycles: twice every day, once every day, twice daily 3 times/week, once daily 3 times/week (page 807, *Methods*). Moreover, Marks et al. teach that 100% of the twice daily treatment cycle had histological clearance, 87.9 % clearance in the once every day regimen, 73.3% clearance in the twice daily 3 times/week regimen, and 69.7% clearance in the once-daily 3 times/week treatment cycle.

Beutner et al. teach a method of treating basal cell carcinoma comprising administering an effective amount of imiquimod 5% cream. With regards to the administration, the reference teaches that 24 patients were treated for at least 6 weeks following 1 of the 5 treatment cycles: twice daily, once per day, three times weekly, twice weekly and once weekly (page 1003, 2<sup>nd</sup> column, *Study Results*). Moreover, Beutner et al. teach that 100% of the twice daily treatment cycle had complete clearance, 100% of the once daily, 100% of the three times weekly, 60% of the twice weekly and 50% of the once weekly (page 1004, 1<sup>st</sup> column, Table II).

Kagy et al. teach a method of treating superficial basal cell carcinomas comprising administering an effective amount of imiquimod 5% cream. With regards to the administration, the reference teaches that one patient was treated for 18 weeks with a once daily application of 5% imiquimod cream, wherein after the 18<sup>th</sup> week the superficial truncal BCC appeared to be eradicated (page 577, Top section, *METHODS* and page 578, 1<sup>st</sup> column, 1<sup>st</sup> full paragraph). In a commentary by John Geisse, the reference teaches that what remains to be defined for imiquimod treatment is the optimal dosing in which there can be three variables: concentration, which at the present time is fixed at 5% by available formulation, the frequency of application, and the duration of course of the therapy (page 578, 1<sup>st</sup> column, 4<sup>th</sup> paragraph of *Commentary*). With regards to the duration of therapy, the reference teaches that the optimal duration would be five out of seven days per week with duration of therapy of about 12 weeks (page 579, 1<sup>st</sup> column, last paragraph). Lastly, the reference

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teaches that further clinical trials are needed to determine the optimal dosing to minimize cutaneous side-effects and maximize efficacy (page 579, 2<sup>nd</sup> column, paragraph bridging 1<sup>st</sup> column).

Marks et al., Beutner et al. and Kagy et al. do not explicitly teach a treatment cycle that comprises at least two consecutive days or at least five consecutive days in which imiquimod is administered and at least one day or 2 days in which imiquimod is not administered. Nor do Marks et al., Beutner et al. and Kagy et al. explicitly teach that the treatment area further comprises skin at least 0.5 cm beyond the margin of the lesion.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the treatment cycle and treatment area for the administration of imiquimod as taught by Marks et al., Beutner et al. and Kagy et al.. One would have been motivated to do so because while each of the references teach successful treatments of basal cell carcinoma, Geisse et al. (Commentary in Kagy et al.) teaches that further clinical trials are needed to determine the optimal dosing to minimize cutaneous side-effects and maximize efficacy. Furthermore, the Courts have found that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. As such, one would have a reasonable expectation of success that by optimizing the treatment cycle or treatment area of imiquimod to at least 2 or 5 days administration of imiquimod and at least one or two days of “rest” and at least 0.5 cm beyond the margin of the lesion, one would achieve an optimal method of treating basal cell carcinoma which minimizes the cutaneous side-effects.

In response to this rejection, Applicants request that the rejections based on Marks et al. and Geisse et al. be withdrawn in view of the affidavit of Mary L. Owens because MPEP 2141.01 states that an obviousness rejection based on a publication which would be applied under 102(a) if it anticipated the claims can be overcome by swearing behind the publication date of the reference by filing an affidavit or declaration under 37 CFR 1.131. Regarding the Beutner et al. and Kagy et al. references, Applicants submit that the Office Action fails to set forth a *prima facie* case of obviousness because *In re Aller* does not apply to the presently claimed subject matter. For example, Applicants submit that the subject matter of claim 1 is not merely selection of optimum regimen from the ranges previously disclosed in the prior art, but represents an entirely new way of thinking about treatment cycles. For example, Applicants submit that, as made evident by the Commentary

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of Dr. Geisse in Kagy et al. cited in the Office Action, one clearly skilled in the art would explore optimizing the dosing by routine experimentation to determine (a) how much drug is administered, (b) how often it is administered (e.g., once, twice, three times, five times, ect. per week), and (c) how long to provide treatment. However, Applicants submit that they have recognized a new variable: the timing of application through the treatment cycle. As such, Applicants submit that in the absence of hindsight derived from Applicants' disclosure, one skilled in the art would not have been motivated to modify the timing of administration within known treatment cycles to arrive at the claimed subject matter. Applicants further submit that the efficacy of the claimed treatment cycle, demonstrated in Fig. 1 and Fig. 2 is an unexpected result: five consecutive days of treatment and two consecutive days of rest provides a response rate that is equal to or better than treatment seven days per weeks. Again, Applicants assert that Dr. Geisse's commentary in Kagy et al. supports Applicants' position that the claimed treatment cycle, which provides reduced adverse side effects compared to seven days of treatment per week, is wholly unexpected. In summary, Applicants assert that the claimed treatment cycle is nonobvious over Beutner et al. and Kagy et al. because the claimed treatment cycle is not taught or suggested by the prior art and is not merely an optimization of ranges because the claimed treatment cycle provides an unexpected result relative to the prior art.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants request that the rejection based on the Marks et al. reference and the Geisse et al. reference be withdrawn in view of the Affidavit of Mary L. Owens, the Examiner has withdrawn the Geisse et al. reference from this rejection because an obviousness based rejection based on a publication which would be applied under 102(a) can be overcome by swearing behind the publication date of the reference by filing an affidavit or declaration under 37 CFR 1.131. However, the Examiner recognizes that the Marks et al. reference was published on May 2001 and thereof, would be applied under 102(b) which is a statutory bar and cannot be overcome by an affidavit or declaration. As such, the Marks et al. reference is maintained. With regards to Applicants assertion that *In re Aller* does not apply to the presently amended claims, the Examiner acknowledges that in *Aller*, the U.S. Court of Customs and Patent Appeals stated that "Normally, change in temperature, concentration, or both, is not patentable modification; however, such changes may impart patentability to process if ranges claimed produce new and unexpected result which is different in kind and not merely in degree from results of prior art; such ranges are termed

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“critical” ranges, and applicant has burden of proving such criticality; even though applicant's modification results in great improvement and utility over prior art, it may still not be patentable if modification was within capabilities of one skilled in art; more particularly, where general conditions of claim are disclosed in prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.” In the instant case, the Examiner recognizes that each of the references teach successful treatments of basal cell carcinoma using a variety of treatment protocols, including different times of application though out the treatment cycle, e.g., how often it is administered. Moreover, as noted in the previous office action, Geisse et al. (Commentary in Kagy et al.) teaches that further clinical trials are needed to determine the optimal dosing to minimize cutaneous side-effects and maximize efficacy and further, that the optimal duration would be five out of seven days per week with duration of therapy of about 12 weeks. Thus, Dr. Geisse et al., one clearly skilled in the art, states that the optimal dosing duration should be five out of seven days per week. While, there is no requirement that an “express, written motivation to combine must appear in prior art references before a finding of obviousness”, motivation to combine prior art references may exist in the nature of the problem to be solved or the knowledge of one of ordinary skill in the art (See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004), Ruiz at 1276, 69 USPQ2d at 1690 and National Steel Car v. Canadlan Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). As such, references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). Regarding Applicants assertion of unexpected results, the Examiner acknowledges Applicants assertion that the claimed treatment cycle, which provides reduced adverse side effects and no dose-dependent reduction in response rate, as compared to seven days of treatment per week is wholly unexpected relative to the prior art. However, it is the Examiners opinion that the evidence of unexpected results is not convincing because one of skill in the art would have reasonable expectation that by optimizing the treatment cycle or treatment area of imiquimod to at least 2 or 5 days administration of imiquimod and at least one or two days of “rest” and at least 0.5 cm beyond the margin of the lesion, one would achieve an optimal method of treating basal cell carcinoma which minimizes the cutaneous side-effects. For example, Dr. Geisse’s commentary in Kagy et al. supports the Office position. Dr. Geisse states (page 578, 1<sup>st</sup> column, last paragraph to 2<sup>nd</sup> column and page 579, 1<sup>st</sup> column, last paragraph):

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“As to the frequency of application, our work clearly demonstrate dose dependent effects particularly in terms of local adverse reactions. In the extreme, with twice daily application under occlusion, we generated ulceration. With decreasing application, to once daily, five time weekly, three times weekly and once weekly, there was a decline in the local adverse events that we noted.”... “In broad terms, our personal opinion is that the optimal dosing would be five out of seven days per week for a duration of therapy of about twelve weeks. Patients should be allowed rest periods during treatment if local reactions become symptomatic. Further clinical trial are needed to determine the optimal dosing to minimize cutaneous side effects and maximize efficacy.”

Thus, in view of Dr. Geisse personal opinion, one of skill in the art would have a reasonable expectation of success that dosing five out of the seven days would provide the optimal dosing which minimizes cutaneous side effects and maximizes efficacy.

Claims 13-15 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Marks et al. (J. Am. Acad. Dermatol. 2001; 44: 807-813) or Beutner et al. (J. Am. Acad. Dermatol. 1999; 41: 1002-1007) or Kagy et al. (Dermatol. Surg. 2000; 26: 577-579) in view of Aldara™ (FDA, Labeling Revision 2001).

Marks et al., Beutner et al. and Kagy et al. teach, as applied to claims 1, 7-12 and 16 above, a method of treating basal cell carcinomas comprising administering an effective amount of imiquimod 5% cream.

Marks et al., Beutner et al. and Kagy et al. do not explicitly teach that the imiquimod cream is applied to the treatment are for about eight hours.

Aldara™ teaches that Aldara™ is the brand name for imiquimod which is an immune response modifier used for the treatment of external genital and perianal warts/condyloma acuminata in adults (page 3 and page 6, Indication and Usage). The labeling revision further teaches (page 12, Dosage and Administration) that Aldara cream should be applied to the target area prior to normal sleeping hours, and left on the skin for 6 to 10 hours.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the imiquimod cream to the treatment area as taught by Marks et al., Beutner et al. and Kagy et al. for about 8 hours in order to optimize the treatment cycle and

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treatment area for the administration of imiquimod. One would have been motivated to do so because the Aldara labeling revision teaches (page 12, Dosage and Administration) that Aldara cream should be applied to the target area prior to normal sleeping hours, and left on the skin for 6 to 10 hours. As such, one would have a reasonable expectation of success that by applying the imiquimod cream to the treatment area as taught by Marks et al., Beutner et al. and Kagy et al. for about 8 hours, one would achieve the optimal time for imiquimod treatment of basal cell carcinoma.

In response to this rejection, Applicants assert that the FDA Labeling Revision is dated after the invention was made, as demonstrated by Exhibit I and Exhibit II to the Affidavit of Mary L. Owens, and therefore, is not prior art to the claimed subject matter and can not be used to cure the deficiencies of Marks et al., Beutner et al. and Kagy et al. to reject the claims under 35 USC 103(a).

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertion that the FDA Labeling revision is not prior art to the claimed subject matter, the Examiner recognizes that the FDA Labeling revision was published on December 8<sup>th</sup>, 2001 and thereof, would be applied under 102(b) which is a statutory bar and cannot be overcome by an affidavit or declaration. As such, the FDA Labeling revision is maintained.

Therefore, NO claim is allowed

**All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.**

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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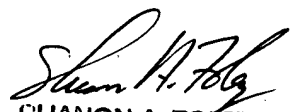
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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